DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/09 has been entered.

Claims 2, 4-9, 15-33 are pending.

Claims 28-29 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 2, 4-9, 15-27 and 30-33 are currently under consideration.

The art rejections are withdrawn in view of applicant's amendment.

The rejection is re-written in view of the addition of claims 31 and 32 to the rejection.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4-9, 15-27 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a

hyperproliferative cells **in vitro** comprising the administration of an inhibitor of a receptor tyrosine kinase ligand (such as a nucleic acid inhibitors, proteins, antibodies, and low molecular weight compounds), does not reasonably provide enablement for a method of treating or preventing a hyperproliferative disease **in vivo** or for increasing the efficacy of therapies or sensitivity of the disorder **in vivo** comprising the administration of an inhibitor of a receptor tyrosine kinase ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of treating a hyperproliferative disorder or for increasing the efficacy of therapies or sensitivity of the disorder **in vivo** comprising the administration of any inhibitor of a receptor tyrosine kinase ligand. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as

chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass the administration of any inhibitor of a receptor tyrosine kinase ligand. This includes inhibitors made from nucleic acid molecules, proteins, antibodies, and low molecular weight compounds. In addition, the claims also encompass using these compounds in vivo. Further, it includes methods of gene therapy, when the inhibitor is a nucleic acid molecule. And finally, the claims encompass the prevention of cancer. There is insufficient guidance and objective evidence that those of skill in the art would be capable of practicing the full scope of the claimed invention i.e. treat or preventing hyperproliferative disorders in an individual using the broad class of any inhibitor of a receptor tyrosine kinase ligand; wherein it would not be predictable to one of skill in the art to use the method in order to treat hyperproliferative disorders in any individual.

The unpredictability of the art and the state of the prior art

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-

cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from

those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

As drawn to the art of anti-cancer therapy in particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that it was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it

could not be predicted, nor would it be expected in the absence of objective evidence in an appropriate model that the claimed invention will function as claimed

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, paragraph 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, paragraph 1). Further, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, paragraph 2). The specification states on page 55 that the highest levels of circulating ductal antigen are

associated with patients with clinical evidence of breast cancer. There is no suggestion in the specification that the expression of these antigens has resulted in autoantibodies against the antigen thus it would be highly unpredictable that administration of the antigen as a cancer vaccine, into patients that already express a heavy load of the antigen in serum, would lead to an effective immune response against the tumor. DeGruijl et al (Nature Medicine, 5410): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. In fact, vaccine compositions would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

And finally with regard to using nucleic acid molecules for the treatment and prevention of hyperproliferative disorders, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky NIH ad hoc committee December 1995 http://www.nih.gov/news/pane/rep.html, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann (Scientific American June 1997, page 96-

101) discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma (Nature 1997 September;389:239-242) states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239).

In an article published well after the effective filing date of the instant application, Rubanyi (Molecular Aspects of Medecine 2001 ;22:113-142) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far …" (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result.

Working examples and Guidance in the Specification

The working examples are limited to using siRNA for the silencing of a particular gene. The specification does not teach the full scope of using any and all inhibitors of receptor tyrosine kinase lignad as claimed. Moreover, the specification does not provide guidance to overcome the unpredictable nature of gene therapy and the use of antibodies in the treatment of cancer or any diseases. Finally, the specification has not provided any correlation between the results obtained the in vitro studies to in vivo efficacy such that the full scope of the claims can be practiced without undue experimentation.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to applicant's arguments

Applicant argues that the in vitro data is correlatable to in vivo use and provides figures from a 2009 WO document. These results are insufficient because there is no indication that the in vitro assays used in the 2009 document are the same as used applicant. Such correlation is needed because in order to provide proper correlation between in vitro assays and in vivo assays in the absence of in vivo results in the original application, the evidence submitted should show the same in vitro assay used by applicant can be correlated to in vivo use. This has not been done. Furthermore, the in vitro assay used by applicant uses siRNA and the reference uses antibodies--thus applicant's assays and the reference assays are using two different inhibitors thus there can be no correlation. Even if applicant had provided proper correlative evidence, this does not address the issues raised in the rejection pertaining the "prevention" and "gene therapy".

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Monday-Thursday 6am to 2pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sheela J Huff/
Primary Examiner
Art Unit 1643

sjh